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HYPOTONIC-HYPORESPONSIVE EPISODES IN CHILDREN HOSPITALIZED AT 10 CANADIAN PEDIATRIC TERTIARY-CARE CENTRES, 1991-1994

Introduction

Hypotonic-hyporesponsive episode (HHE), sometimes called the ragdoll, collapse reaction, or shock-like state refers to an adverse event occurring after administration of whole-cell pertussis vaccine; the infant becomes pale and displays decreased responsiveness, muscle tone, and activity. Although HHE occurs most often after immunization with whole-cell pertussis vaccine, it has also been reported with lower frequency after diptheria-tetanus (DT) and acellular pertussis-DT vaccine. In a prospective study of 15,752 diptheria and tetanus toxoids, and pertussis (DPT) immunizations in the United States, the incidence of HHE was found to be 1 in 1,750 immunizations[1]. Although HHE is often very disturbing to parents and physicians, long-term follow-up suggests that neurologic sequelae do not occur[2].

About 350 HHE cases are reported to Health Canada annually through the passive surveillance system for vaccine-associated adverse events (VAAEs), but cases in Canada have not previously been described in detail[3]. The Immunization Monitoring Program, Active (IMPACT), the active surveillance system coordinated by the Canadian Paediatric Society and sponsored by the Laboratory Centre for Disease Control, was used to analyze data collected on cases hospitalized at 10 Canadian pediatric tertiary-care centres between 1 January 1991 and 31 December 1994[4,5]. Five centres started surveillance in mid-1993.

Methods

Active surveillance for cases of HHE was carried out at British Columbia's Children's Hospital, Vancouver; Alberta Children's Provincial General Hospital, Calgary; Health Sciences Centre, Winnipeg; The Hospital for Sick Children, Toronto; Children's Hospital of Eastern Ontario, Ottawa; The Montreal Children's Hospital, and *Hôpital Sainte-Justine*, Montreal; *Centre hospitalier de l'Université Laval*, Quebec; IWK Grace Health Centre for Children, Women, and Families, Halifax; and The Dr. Charles A. Janeway Child Health Centre, St. John's[2,3]. For purposes of case finding, HHE was defined as the sudden onset of two or more of the following within 48 hours of administration of whole-cell pertussis vaccine: pallor, cyanosis, hyporesponsiveness, or decreased muscle tone. IMPACT investigators confirmed that the surveillance criteria were met for each case. Data on each case were collected on a standardized form. Immunization history was obtained from immunization records from parents, the child's family physician, or a local medical officer of health. Reports were assessed for completeness and entered into a computerized database at the Vaccine Evaluation Centre in Vancouver.

Results

Between 1 January 1991 and 12 March 1994, 10 infants < 2 years of age were hospitalized at seven of the 10 pediatric centres (Table 1). All 10 infants were in good health and without underlying medical problems prior to occurrence of HHE. Six of the episodes occurred after the first vaccination at 2 months of age, two after the second vaccination at 4 months of age, and two after the third dose at 6 months of age.

All children received a combined vaccine containing whole-cell pertussis vaccine. Four received DPT combined with *Haemophilus influenzae* b-CRM conjugate (HibTITER™) vaccine and oral polio vaccine (OPV), three received DPT and OPV, two received DPT-inactivated polio vaccine (IPV) combined with *Haemophilus influenzae* b-tetanus toxoid conjugate (PENTA™) vaccine, and one received DPT-IPV alone.

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Table 1
Distribution of cases of HHE at seven IMPACT centres

Pediatric Centre	Location	No. of cases of HHE
British Columbia's Children's Hospital	Vancouver, BC	1
Health Sciences Centre	Winnipeg, MB	1
The Hospital for Sick Children	Toronto, ON	1
Children's Hospital of Eastern Ontario	Ottawa, ON	1
The Montreal Children's Hospital	Montreal, QC	3
IWK Grace Health Centre for Children, Women, and Families	Halifax, NS	1
The Dr. Charles A. Janeway Child Health Centre	St. John's, NF	2

The time of onset of symptoms was available for all cases (Table 2); HHE began a median of 3 hours after vaccination. Onset was < 6 hours in seven of 10 cases. The longest interval between vaccination and onset of HHE was 48 hours. The duration of the episode was reported in eight of 10 cases. Most of the episodes were brief: episodes were < 10 minutes in five infants and 30, 60, and 120 minutes in the other three infants, respectively. One infant had two more brief episodes in hospital. Pallor was the most common symptom, occurring in nine infants, followed by limpness in seven, circumoral cyanosis in seven, and hyporesponsiveness in five. The mean temperature at admission was 38.4° C. Only two infants had fever > 39.0° C. Blood pressure was normal at admission in all tested infants. Blood glucose was normal in seven infants in whom it was measured. Neurologic examination was normal, other than transient hyporesponsiveness and hypotonicity. All infants were normal at the time of discharge from hospital. Duration of hospitalization was brief: six infants were in hospital for ≤ 1 day, two for 2 days, and two for 5 days.

Follow-up information was obtained by telephone contact with the parents of eight infants at a mean of 26.5 months after the episode (range: 4 to 52 months); the parents of each of these infants reported that their development was normal. None of the infants experienced similar spells during the follow-up period with subsequent immunizations or otherwise. Pertussis vaccine was omitted from all subsequent immunizations.

Table 2
Clinical features of cases of HHE at seven IMPACT centres

Finding	No. of cases with confirmed observations	No. of cases with observations as reported
Pallor	9	10
Hypotonicity	7	9
Hyporesponsiveness	5	10
Perioral cyanosis	7	9
Normal blood pressure on admission	5	5
Normal blood sugar on admission	7	7
Normal neurologic exam at discharge	10	10

Discussion

IMPACT was designed to detect VAAEs severe enough to result in hospitalization. The features of the 10 cases of HHE detected in the first 3 years of IMPACT surveillance are similar to those described in the prospective study of Cody et al[1]. IMPACT can not determine the incidence of HHE because it is a case-finding surveillance system at 10 pediatric tertiary-care hospitals; it does not draw from a defined population base. Total admissions during the surveillance period exceeded 200,000, placing the hospitalization rate at < 1 HHE case per 20,000 admissions. Moreover, the mild nature of most of the 10 episodes suggests that hospital-based surveillance may not detect all cases. Many appear so mild that, even if parents do seek medical care, the child will not be hospitalized. Recent expansion of case-finding to include emergency rooms at IMPACT hospitals may enable more complete case finding.

Although follow-up was limited to one telephone contact with the parents of each infant, 1 to 2 years after the event, no developmental or other neurologic problems were reported.

The etiology of HHE remains unknown. Its features are consistent with infant fainting spells, perhaps triggered by injection-site pain and/or fever. There do not appear to be any long-term neurologic sequelae. Additional studies on larger numbers of infants with HHE will be required to confirm the benign nature of this event.

Acknowledgements

The diligence of IMPACT nurse monitors, coordinators, and other staff is gratefully acknowledged. IMPACT is funded by the Immunization Division, Bureau of Infectious Diseases, Laboratory Centre for Disease Control, Ottawa, ON.

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2. Baraff L, Shields W, Beckwith L et al. *Infants and children with convulsions and hypotonic-hyporesponsive episodes following diphtheria-tetanus-pertussis immunization: follow-up evaluation*. J Pediatr 1988;81:789-94.
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4. Members of the LCDC/CPS IMPACT Group. *IMPACT monitoring network: a better mousetrap*. Can J Infect Dis 1993;4:75-6.
5. Scheifele D, Gold R, Law B et al. *Decline in **Haemophilus influenzae** type b invasive infections at five Canadian pediatric centres*. CCDR 1993;19:88-91.

Source: *R Gold, MD, D Scheifele, MD, S Halperin, MD, P Déry, MD, B Law, MD, M Lebel, MD, N MacDonald, MD, E Mills, MD, R Morris, MD, T Jadavji, MD, (IMPACT members), V Marchessault, MD, (CPS Liaison), P Duclos, DVM, PhD, (LCDC Liaison).*

Editorial Comment

From 1991 to 1994, 1,371 cases of HHE had been reported to Health Canada's Vaccine-Associated Adverse Events Surveillance System (VAAESS). This is an estimated rate of one case per 6,000 vaccinations with DPT or DPT-Polio, which is within the incidence estimates of one case to every 344 to 28,500 vaccinations reported in studies reviewed by the Institutes of Medicine in the United States[1], especially with underreporting taken into account. Dr. Gold and colleagues presented specific details on 10 cases of HHE identified by IMPACT over the same period of time. Since IMPACT is designed to capture the most serious adverse events related to vaccination, these 10 cases are representative of the more severe manifestations of HHE. Despite this, follow-up of the children 1 to 2 years of age did not later reveal any sequelae. This finding is very reassuring. Despite the small number of cases, it adds to the body of evidence pointing to HHE as a benign reaction[1], despite the fact that it can be very frightening for parents to witness and that it remains of unexplained etiology.

For those reasons, HHE is still a relative contraindication to further immunization with pertussis vaccine[2]. Gold and colleagues noted that none of the children hospitalized with HHE completed their series. The Canadian Immunization Guide suggests continuing vaccination when the incidence of disease warrants it[2], but that determination is a very difficult one to make. Data are still lacking on the incidence of second episodes of HHE and their sequelae in children who have continued their pertussis series. (There are only a few anecdotal reports from one Canadian province where four children were successfully reimmunized with no repeat HHE.) In the not too distant past, HHE used to be an absolute contraindication to further vaccination. It is not surprising that none of the children were considered for continued immunization. Unfortunately, in more recent years, there has been a marked resurgence of pertussis in several parts of the country. It would be interesting to find out how many infants are continuing to receive pertussis vaccine after HHE.

We may be reassured with the advent of the newer acellular pertussis vaccines. The incidence of HHE appears to be considerably less with these products. Children who have had an episode with the whole-cell vaccine may now be more readily considered for continued immunization. The advent of these vaccines notwithstanding, we still need to improve the recognition of HHE (a case definition was described in the report by Gold and colleagues) and the counselling of parents about what to expect as potential side effects to vaccination, in order to diminish any fear of vaccination that may arise. Finally, we need to collect more follow-up data on children who have experienced HHE to be able to more definitively reassure both parents and health-care providers about the significance of these events. The IMPACT project will continue to monitor and follow-up the more serious cases of HHE, and also expand monitoring to some of the less severe cases, such as those seen in emergency rooms or short-stay units; the national VAAESS will continue to collect and specially review cases from the voluntary reporting system. All these efforts will hopefully continue to shed more light on this unusual, but significant adverse event related to immunization.

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2. National Advisory Committee on Immunization. *Canadian immunization guide*. 4th ed. Ottawa, ON: Health Canada, 1993. (Supply and Services Canada, Cat. No. H49-8/1993E.)

RESPIRATORY VIRUS SURVEILLANCE
FluWatch Project

Influenza-like illness (ILI) reported by sentinel physicians to FluWatch started to decrease in mid-March. The rates have now returned to those seen in the early fall of 1996 (Figure 1). Laboratory data have confirmed that the first wave of influenza activity was associated with influenza A and reached its peak in mid-January (Figure 2). A second wave associated with influenza B began in February and is now almost over (Figure 3).

Up to 14 April 1997, a total of 216 influenza isolates have been characterized at the Laboratory Centre for Disease Control. One hundred and sixty-nine of them are influenza A viruses; 168 are A/Wuhan/359/95 (H3N2)-like and one is A/Johannesburg/33/94 (H3N2)-like. Forty-seven are influenza B viruses identified from the isolates submitted to this laboratory; all of them are B/Beijing/184/93-like.

Figure 1
Standardized rates of ILI across Canada by 2-week periods, reported to FluWatch, 26 October 1996 - 6 April 1997

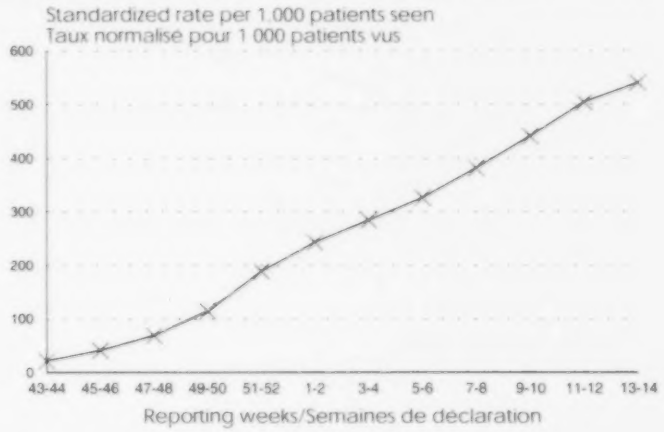


Figure 2
Positive Influenza A tests in Canada, by region and by week of report

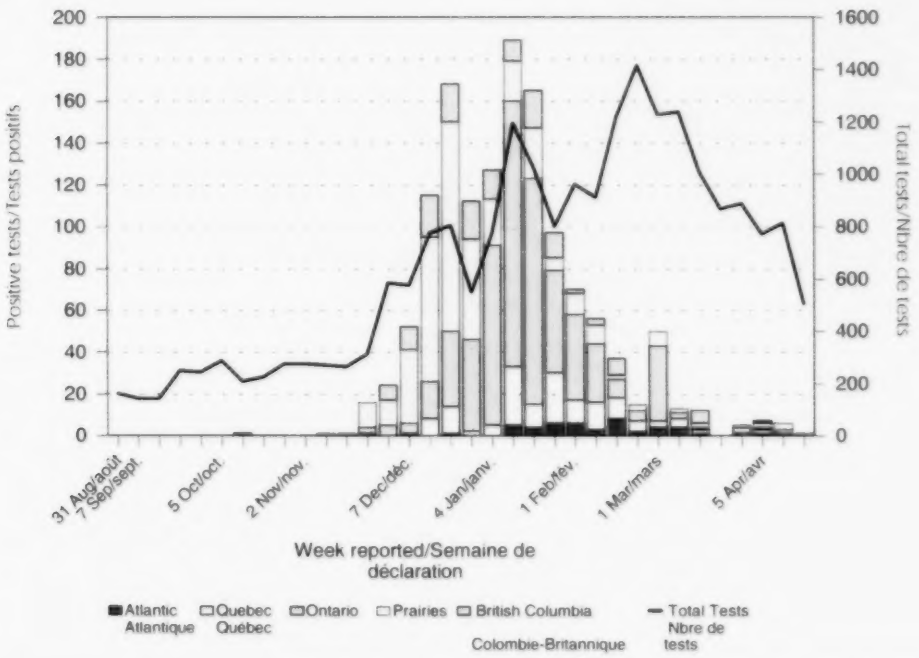
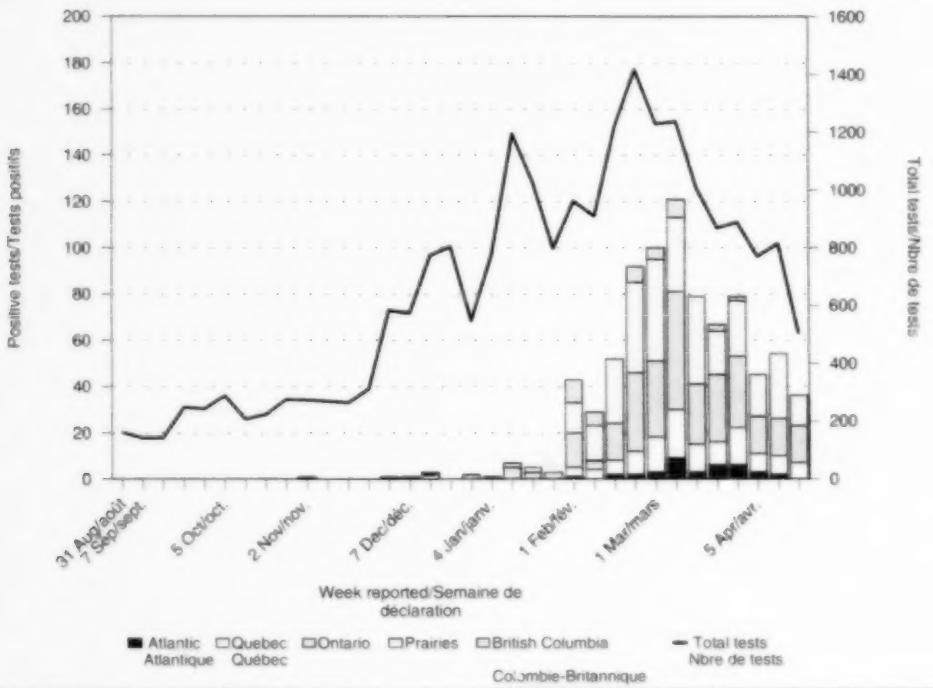


Figure 3
Positive Influenza B tests in Canada, by region and by week of report



Source: *Division of Disease Surveillance, Bureau of Infectious Diseases, LCDC, Ottawa, ON.*

International Notes

INFLUENZA ACTIVITY — UNITED STATES, 1996-1997 SEASON

Influenza activity in the United States has continued to decline since mid-January 1997. The predominant viruses have been influenza type A (H3N2), although the proportion of influenza B isolates has increased since the week ending 18 January. This report summarizes influenza activity in the United States from 29 September 1996, through the week ending 15 February 1997.

The proportion of patients who visited 120 U.S. sentinel physicians for influenza-like illness (ILI) peaked at 7% from mid-December through the first week of January and was 3% of total visits by the week ending 15 February 1997. The proportion of visits for ILI had remained at or below the baseline level of 3% since the week ending 25 January 1997; however, the proportion of ILI visits had not yet reached baseline levels in the West South Central and Pacific regions through the week ending 15 February 1997.

Influenza activity has decreased since the week ending 28 December 1996, when state and territorial epidemiologists in 38 states reported either widespread or regional activity. For the week ending 15 February 1997, either widespread or regional influenza activity was reported in 21 states and sporadic activity was reported in 25 states and the District of Columbia (Figure 1). None of the states in the East North Central region reported regional or widespread activity for the week ending 15 February.

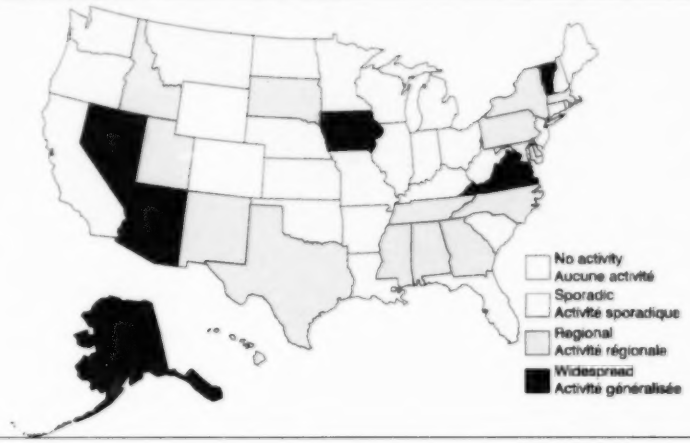
The proportion of deaths attributed to pneumonia and influenza among 122 U.S. cities exceeded the epidemic threshold[*] during the week ending 14 December 1996, and peaked at 9.1% during the week ending 25 January 1997. Since then, although the proportion of pneumonia and influenza deaths has declined, it has remained above the epidemic threshold for 10 consecutive weeks through the week ending 15 February 1997 (Figure 2).

From 29 September 1996, through 15 February 1997, World Health Organization collaborating laboratories in the United States reported 5,050 (19.1%) influenza isolates from the total 26,430 specimens submitted for respiratory virus testing: 4,714 (93.4%)

were type A, and 336 (6.7%) were type B. All 1,866 influenza A isolates subtyped have been A (H3N2) viruses; thus far, no A (H1N1) viruses have been reported in the United States during the 1996-97 influenza season. From 29 September 1996, through 28 December 1996, a total of 38 (1.4%) of 2,811 influenza isolates were type B. Although the total number of influenza viruses isolated has declined since then, the proportion of influenza B isolates has increased. From 26 January to 15 February, a total of 166 (42.5%) of the 391 reported influenza isolates were type B. At least one type B isolate has been reported from each region.

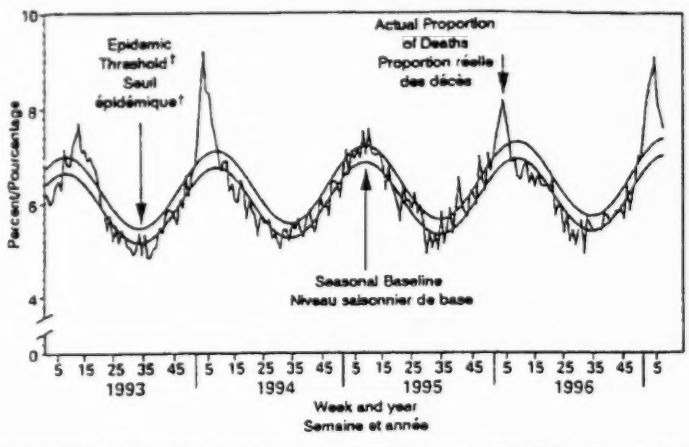
Source: *Morbidity and Mortality Weekly Report, Vol 46, No 8, 1997.*

Figure 1
Levels of influenza activity* reported by state and territorial epidemiologists — United States, week ending 15 February 1997



* Levels of activity are 1) *no activity*, 2) *sporadic*—sporadically occurring ILI or culture-confirmed influenza with no outbreaks detected; 3) *regional*—outbreaks of ILI or culture-confirmed influenza in counties with a combined population of < 50% of the state's total population; and 4) *widespread*—outbreaks of ILI or culture-confirmed influenza in counties with a combined population of ≥ 50% of the state's total population.

Figure 2
Weekly pneumonia and influenza mortality as a percentage of all deaths in 122 cities — United States, 1 January 1993 - 15 February 1997



†† The epidemic threshold is 1.645 standard deviations above the seasonal baseline. The expected seasonal baseline is projected using a robust regression procedure in which a periodic regression model is applied to observed percentages of deaths from pneumonia and influenza since 1983.

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